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| 10/649,413 | 08/27/2003 | Axel Ullrich | 224160 | 5257 |

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EXAMINER

SHAHER, SHULAMITH H

| ART UNIT | PAPER NUMBER |
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1647

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|---|---------------------------------------|--|
| Office Action Summary | Application No. 10/649,413 | Applicant(s) ULLRICH ET AL. | |
| | Examiner Shulamith H. Shafer, Ph.D. | Art Unit 1647 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 15-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>8/27/03</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Status of Application, Amendments, And/Or Claims

Applicant's election, with traverse, of the claims 1-14 in Group I, drawn to a method of treatment of an RTK-hyperfunction disorder, filed on 9 March 2006 in response to the 13 January 2006 office action is acknowledged. The traversal is on the ground(s) that the examination of the entire application would not constitute a burden to search because of the alleged overlapping of the searches for groups I-V. This is not found persuasive because while the searches for the different inventions may overlap in part, searching all of these inventions together would constitute a serious search burden for reasons set forth in the Office Action of 13 January 2006. Contrary to applicants' assertion that any search of the prior art in regard to Group I will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-29 are pending in the instant application. Claims 15-29 are withdrawn from consideration as being directed to a non-elected invention. Claims 1-14 are under examination.

Art Unit: 1647

Objections

Specification:

The disclosure is objected to because of the following informalities: Application 09/600,826 is now issued patent US 6,770,742. The first line of the specification should include an updated cross-reference to related applications.

Information Disclosure:

Reference AK of IDS filed 27 August 2003 are not in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 for the following reasons: This reference was not submitted to the Office; it is therefore lined through, and has not been considered. Reference AQ is in Japanese; no translation of the abstract or explanation of relevance was included. It is therefore lined through, and has not been considered.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, the independent claim of the instant invention recites "inhibitor of fibroblast growth factor receptor-4 (FGFR-4)". The claim is indefinite because it is not clear whether applicant intends the FGFR-4 gene or the FGFR-4 protein.

Claim 1 recites a "(RTK)-hyperfunction-induced disorder". Claim 2 goes on to recite a number of disorders. It is unclear how "a disorder" can be "one or more" disorders.

Claim 2 recites a disorder "selected from the group consisting of cancer,a carcinoma and a metastasis". A metastasis is not a specific disease or disorder.

If Claim 1 is drawn to the FGFR-4 receptor protein, Claims 5-6 are vague and indefinite because they fail to further limit Claim 1.

Claim 6 recites "a mutation"; Claim 7 recites "wherein the mutation is one or several point mutations". It is unclear how "a mutation" can be "one or several point mutations".

Claim 11 is vague and indefinite in the recitation of "amino acid position 388 in the FGFR-4 molecule". No direction is provided as to the sequence in which the amino acid in position 388 is mutated. Without a reference to a specific sequence, a residue of a given number is indefinite.

Claims 3-5, 8-10, and 12-14 are included in this rejection as being dependent from rejected claims.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for:

A method for the therapeutic treatment of a receptor tyrosine kinase (RTK)-hyperfunction-induced disorder in a mammal which method comprises administering to a mammal an effective amount of at least one inhibitor of mutated fibroblast growth factor receptor-4 (FGFR-4) protein activity wherein the mutation is in the transmembrane domain of FGFR-4 protein at position 388 in which a glycine amino acid is substituted for an arginine amino acid, the sequence of which is deposited in the EMBL Gene Bank/DDBJ under X57205

does not reasonably provide enablement for:

A method for the prophylactic treatment of a receptor tyrosine kinase (RTK)-hyperfunction-induced disorder in a mammal which method comprises administering to a mammal an effective amount of at least one inhibitor of fibroblast growth factor receptor-4 (FGFR-4) protein activity or expression or at least one inhibitor of fibroblast growth factor receptor-4 gene expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When

Art Unit: 1647

determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claim 1, the independent claim of the instant invention, is a method for prophylactic treatment of a RTK-hyperfunction-induced disorder in a mammal. However, the phrase "prophylactic treatment", given its broadest reasonable interpretation with the specification, requires that absolutely no cell, nor tissue, would present any symptom of a disorder after treatment with an inhibitor of the mutated FGFR-4 receptor. There is no evidence in the specification or in the prior art, that any method to date can accomplish this goal. The specification presents the results of several experiments demonstrating that the expression of mutated FGFR-4 receptor is elevated in certain diseased tissues; however, there is no support for the prophylactic treatment of any disorder, as is required by the claims, and neither can such support be obtained through reasonable extrapolation of the data. Thus, one skilled in the art clearly would not know how to use the claimed invention for "prophylactic treatment" of a disease.

The claims, given their broadest reasonable interpretation, are directed to a method of treatment encompassing administration of inhibitor of FGFR-4 receptor activity and/or expression. The claims encompass wild-type FGFR-4 proteins and mutated FGFR-4 polypeptides which can have any, unspecified numbers of substitutions, insertions and/or deletions. The specification discloses a correlation between expression of the mutated FGFR-4 receptor protein, the mutation being a point mutation in the amino acid 388 wherein glycine is replaced by arginine, and increased incidence of lymph metastases and decreased relapse-free survival time (page 28, paragraphs 1-3, and Figures 4 and 5). Applicants conclude that "the FGFR-4 mutation G388R leads to a 2.7-fold increased risk for metastasis formation in the lymph nodes

Art Unit: 1647

and to a 5.44-fold increased risk of a tumour relapse. [Breast cancer] Patients with a mutated FGFR-4 allele (G388R) thus seem to have a predisposition to a tumour relapse and hence a poorer disease prognosis". The art teaches this particular mutation is associated with increased motility in MDA-MB-231 mammary tumor cells (2002, Bange et al. Cancer Res. 62:840-847, abstract) and with poor clinical outcome in head and neck squamous cell carcinoma (2004, Streit et al. Int J Cancer 111:213-217, abstract). The art teaches away from a correlation between expression of the wild-type FGFR-4 and poor prognosis. Streit et al. teach (2002, Proceedings of the American Association for Cancer Research, 43:829, Abstract 4116) that expression of the wild-type FGFR-4 receptor does not correlate with overall survival. The specification does not provide any guidance to making or using mutants other than the FGFR-4 mutation G388R in the methods of the instant invention. There is no teaching as to what other structural changes can be made and still result in a protein associated with increased risk of metastasis and poor clinical outcome. It is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall conformation of the protein molecule. For example, Ratisoontorn et al. (2003, Connective Tissue Res. 44, Suppl1:292-297, abstract) teach that a C278F mutation of FGFR-2 causes a constitutive activity, stimulating cell proliferation and inhibiting mineralization; in contrast, a P253R mutation of the same molecule does not result in ligand-independent activation of the receptor, shows a weak mitotic effect and does not inhibit mineralization. Since the specification does not define which mutations will result in a protein having the same activity as the FGFR-4 mutation G388R receptor protein, undue experimentation would be required to utilize proteins other than the FGFR-4 Arg³⁸⁸ variant in the methods of the instant invention.

Due to the large quantity of experimentation necessary to generate the infinite number of variants of the FGFR-4 protein recited in the claims and possibly screen same for correlation with increased metastasis and poor clinical outcome, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide the required activity, the absence of working examples

Art Unit: 1647

directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the lack of predictability for any prophylactic treatment, and the breadth of the claims which fail to recite any structural limitations undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-11, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treatment comprising administering an effective amount of an inhibitor of FGFR-4. Due to the open claim language, the claims encompass inhibition of the wild-type FGFR-4 and mutated FGFR-4 polypeptides which can have any, unspecified numbers of substitutions, insertions and/or deletions in the methods of the instant invention. Applicant has described a mutated FGFR-4 polypeptide, which has a point mutation in the amino acid 388 wherein glycine is replaced with arginine. Applicant has not described other mutants and variants of FGFR-4 which possess the same properties of the FGFR-4 mutation G388R. There is no teaching regarding which other changes in the protein can lead to a protein associated with increased risk of metastasis and poor clinical outcome. There is no teaching regarding which changes in the protein can lead to increases in receptor tyrosine kinase activity and increased risk of metastasis and poor clinical outcome. Thus, the claims encompass a method comprising inhibition of activity of a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the molecule that Applicant has disclosed.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of

Art Unit: 1647

making the claimed product or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed method comprising administration of an inhibitor of the broadly described FGFR-4 genus of molecules.

Furthermore, Claim 1, the independent claim of the instant invention, is broadly directed to a method for treatment of an RTK-hyperfunction-induced disorder. Cells contain many more tyrosine kinase receptors than the FGFR-4 receptors; there are a large number of RTK-hyperfunction-induced disorders not described in the specification. The claim, as written encompasses any disease associated with aberrant, hyperactivity of an RTK, including any condition characterized by excessive cell growth. The specification discloses that FGFs, the ligands for FGFR's play a major part in cardiovascular diseases, tissue injury, neurobiology, as well as tumorigenesis (page 2, last paragraph). Applicants have disclosed that patients with a point mutation in FGFR-4 at the amino acid 388 wherein glycine is replaced with arginine, resulting in a constitutively active receptor, seem to have a predisposition to a tumor relapse and a poorer disease prognosis. The art teaches this particular mutation is associated with poor clinical outcome in patients with head and neck squamous cell carcinoma (see art cited above). However, the specification does not teach any other disorders associated with RTK-hyperfunction.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

Art Unit: 1647

method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method of treatment of RTK-hyperfunction-induced disorder, wherein the disorder is a cancer, but not any RTK-hyperfunction-induced disorder or any disease attributable to cellular hyperproliferation meets the written description provision of 35 U.S.C. 112, first paragraph. Additionally, the method comprising administration of an inhibitor of activity of a mutated FGFR-4 which has a point mutation in the amino acid 388 wherein glycine is replaced with arginine, but not the administration of an inhibitor to any mutants and variants, meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Takahashi et al. (1991, FEBS 288:65-71). Claim 1, the independent claim of the instant

Art Unit: 1647

invention recites "A method for the prophylactic and therapeutic treatment of a receptor tyrosine kinase (RTK)-hyperfunction-induced disorder in a mammal.....". The method steps disclosed comprise administering to a mammal of an inhibitor of fibroblast growth factor receptor 4 (FGFR-4). Claims 2 and 3 recite a disorder from the group consisting of cancer, a disease attributable to cellular hyperproliferation and/or cellular invasion of tissue, a carcinoma, and a metastasis; claim 3 recites the further limitation of the disorder being breast cancer, squamous cell carcinoma, glioblastoma, neuroblastoma or uterine cancer. Claim 5 recites the further limitation of the receptor activity being inhibited.

The art teaches the FGFs constitute a large family of heparin-binding factors consisting of at least 22 members in mammals (for exemplary purposes, see 2003, Ensoli et al. Chapter 31 *in* The Cytokine Handbook, 4th edition, pages 747-781, page 748, column 2, 1st paragraph) and recognizes that most FGF's bind to all four receptors (for exemplary purposes, see 1999, Klint et al. Front Biosci 4:d165-177, page 177, column 2, 1st paragraph). The specification teaches that "it is difficult to determine the action of a specific ligand on a specific receptor" (page 3, 2nd paragraph). Takahashi et al. teach the subcutaneous administration of a neutralizing antibody against human FGF (unspecified in the reference) to nude mice bearing human glioblastoma cells (page 66, column 2, paragraph 3.5). Administration of this antibody suppresses tumor-development in nude mice (page 67, column 2, 2nd paragraph). Therefore, given the broad language of the claims, the recognition in the art that there is an overlapping pattern of FGF to FGFR's and that most FGF's bind to all four receptors, and absent evidence to the contrary, the FGF taught by Takahashi et al. would bind to the FGF4 receptor of the instant invention. Administration of an antibody to FGF would inhibit the ability of FGF to bind and activate its cognate receptor. Thus, the teachings of Takahashi et al. anticipate all the limitations of claims 1-3, 5 and 14.

Conclusions

No claims are allowed.

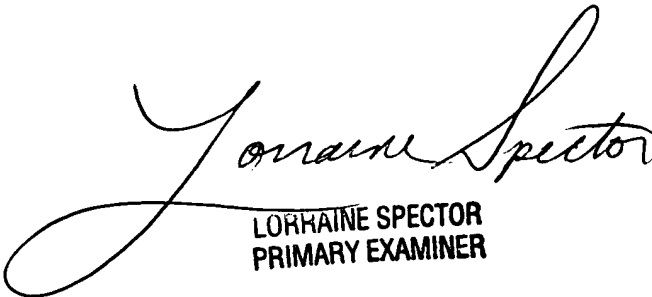
Art Unit: 1647

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the latent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHS


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PRIMARY EXAMINER